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CERTIFICATE OF FACSIMILE
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I hereby certify that this correspondence is being sent via facsimile to Examiner Harry J. Guttman, Ph.D. at (703) 308-4242 with the United States Patent and Trademark Office on the date below:

December 20, 2001
Date

Steven L. Highlander

Commissioner for Patents
Washington, DC 20231

RE: *SN 09/350,327 "HIGH PRESSURE REFOLDING OF PROTEIN AGGREGATES AND INCLUSION BODIES" – By Theodore W. Randolph et al.*

Commissioner:

Enclosed for filing in the above-referenced patent application is:

1. Supplemental Request For Reconsideration Under 37 C.F.R. §1.116;

2. Second Declaration of Theodore W. Randolph.

Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10024085.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642

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Encl.:

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Richard St. John, Ph.D. (w/encl.)

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Theodore W. RANDOLPH *et al.*

Serial No.: 09/350,327

Filed: July 9, 1999

For: HIGH PRESSURE REFOLDING OF PROTEIN AGGREGATES AND INCLUSION BODIES

Group Art Unit: 1651

Examiner: H. Guttman

Atty. Dkt. No.: UTEC:003/SLH

OK to enter HHG Jan 14 2002

SUPPLEMENTAL REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.116

Commissioner for Patents
Washington, D.C. 20231

Sir:

This is further in response to the Office Action mailed on July 31, 2001, the deadline for response having been extended to January 30, 2002, by the previously filed Notice of Appeal, and payment of fees. Should any fees be due, applicants authorize the Commissioner to debit Fulbright & Jaworski Deposit Account No. 55-1212/10024085/SLH. Please date stamp and return the enclosed postcard as proof of receipt.

REMARKS

I. Status of Claims

Claims 1-10, 21 and 22 are pending and stand rejected under the first paragraph of §112. Claims 1-3 stand rejected under §102 over Zong *et al.* ("Zong").

II. Declaration

In the response filed on November 30, 2001, applicants intended to submit a second declaration from Dr. Ted Randolph, one of the inventors. Inadvertently, a copy of a previously submitted declaration was refiled. The undersigned has spoken to the examiner regarding this mistake, and the declaration applicants intended to file with that response is now submitted. Any inconvenience caused to the examiner is regretted.

III. Additional Comment on the Rejection Under 35 U.S.C. §112, First Paragraph

One of the important points raised in the final Office Action was the that the examiner felt that more than the interferon-γ example (in the previously provided affidavit) was needed to support the "two step" process claimed. However, it should be pointed out that, in the original application, under Example 3, it is stated that "samples were slowly pressurized (over 10 minutes) to the final desired pressure .... The depressurization rate was approximately 10 bar/ minute." This method was applied to all three proteins described in the application (recombinant human growth hormone, β-lactamase, and lysozyme), as well as to interferon-γ, as described in the first affidavit of Dr. Randolph. Thus, during the step when pressure was reduced from 2000 bar to 250 bar, the proteins were incubated in the pressure range given in step (d) of claim 1 for 175 minutes, an incubation time that falls within the claimed range of 0.1 to 12 hours.

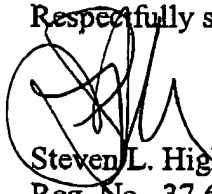
Further, it is noted the "two step" process that is described in the Examples now has been applied to four distinct classes of proteins (a) a disulfide-bonded, catalytically active protein which contains both α-helix and β-sheet (lysozyme); (b) a four-α-helix bundle hormone that binds metals and cell receptors (recombinant human growth hormone); (c) a homodimeric, α-helical protein cytokine (interferon-γ); and (d) a β-sheet, α-helix enzyme that catalyzes degradation of antibiotics and is important in bacterial drug resistance (β-lactamase). This illustrates an additional point, namely, that the methods can be applied to a variety of different protein structures.

Thus, applicants again submit that the present application provides a sufficient basis for finding the present claims enabled. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Conclusion

In light of the foregoing, it is respectfully submitted that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Guttman have any questions, he is invited to contact the undersigned attorney at (512) 536-3184.

Respectfully submitted,



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CLEAN COPY OF CLAIMS (UNOFFICIAL)

1. A method for producing disaggregated biologically active protein from a mixture comprising aggregated protein comprising the steps of:

   (a) adjusting total protein concentration in the mixture to from about 0.01 mg/mL to about 500 mg/mL; then

   (b) increasing the pressure on the mixture to from about 0.25 kbar to about 12 kbar for a time and temperature sufficient for disaggregation of the protein; then

   (c) incubating the mixture under pressure in the range from about 0.25 kbar to about 3.3 kbar for a time from about 0.10 to about 12 hours; then

   (d) reducing the pressure to atmospheric pressure, whereby aggregated protein in the mixture is disaggregated and biological activity is retained.

2. The method of claim 1, wherein during the incubations step (c), the mixture further comprises an oxidizing agent and a reducing agent wherein the oxidizing agent is oxidized glutathione and the reducing agent is dithiothreitol.

3. The method of claim 1, wherein the pressure in the incubation step (c), is from about 0.5 kbar to about 3.3 kbar.

4. The method of claim 3, further comprising adding, prior to step (b), a chaotropic agent at a concentration of from about 0.1 to about 8 M.

5. The method of claim 4, wherein during the incubation step (c), the protein concentration is from about 1 to about 100 mg/mL.

6. The method of claim 4, wherein during the incubation step (c), the protein concentration is from about 1 to about 20 mg/mL.

7. The method of claim 4, wherein after step (c), the concentration of the chaotropic agent is decreased to less than about 0.1 M.

8. The method of claim 1, wherein, prior to step (a), the aggregated protein is treated with a reducing agent.

9. The method of claim 1, wherein the mixture of protein in step (a) comprises a detergent.

10. The method of claim 9, wherein the detergent is selected from the group consisting of sodium dodecyl sulfate, polyethoxysorbitan, deoxycholate, sodium octyl sulfate, sodium tetradecyl sulfate, polyoxyethylene ethers, sodium cholate, octylthioglucopyranoside, n-octylglucopyranoside, alkyltrimethylammonium bromides, alkyltrimethyl ammonium chlorides, and sodium bis (2-ethylhexyl) sulfosuccinate.

21. The method of claim 4, wherein the chaotropic agent is guanidine hydrochloride.

22. The method of claim 21, wherein guanidine hydrochloride is present at a concentration of from about 0.1 to about 1 M.

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